MedinCell

[redacted]

A multicentre randomised, Double-Blind, Placebo-controlled, **S**tudy to evaluate the effic**A**cy and safety of oral **IVE**rmectin tablets in the prevention of COVID-19 (the **SAIVE** Trial)

Protocol Number:	mdc-TTG-CT-002
Investigational Medicinal Product:	Ivermectin
Indication:	SARS-CoV-2 infection
Phase:	II
Sponsor:	MedinCell SA 3 rue des Frères Lumière 34830, Jacou, France
Coordinating Investigator	Dr. Anna Kostova
EudraCT Number:	2021-001938-19
Protocol Version and Date:	Final version 3.0, 08 June 2022

The study will be conducted according to the protocol and in compliance with Good Clinical Practice (GCP), with the Declaration of Helsinki, and with other applicable regulatory requirements.

CONFIDENTIAL INFORMATION

Protocol Approval

Sponsor:

[redacted]

2022-06-17 | 11:08:22 CEST

Signature Date

Coordinating Investigator:

Dr. Anna Kostova
University Hospital" Queen Joanna - ISUL", COVID-19 Department
1527 Sofia Center, Sofia, Bulgaria

DocuSigned by:
Anna Kostova Kostova
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2022-06-17 | 08:05:01 CEST

Signature Date

[redacted]

Site Principal Investigator Agreement

I, _____, (Investigator's Name) have read this protocol and agree that it contains all necessary details for carrying out this trial. I will conduct the trial as outlined herein and will complete the trial within the time designated.

The information contained in this protocol is provided to me in confidence, for review only by myself, the ethics committee authorised to review and approve the trial at this trial site, and designated trial staff participating in this clinical trial.

I agree to the conditions as set out in this protocol and fully accept that any change requires prior approval by the trial sponsor.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this trial. I will discuss this material with them to ensure they are fully informed regarding the IMP and the conduct of the trial.

I will use only the informed consent form approved by the sponsor or its representative and will fulfil all responsibilities for submitting pertinent information to the Institutional Review Board/Independent Ethics Committee (IRB/IEC) responsible for this trial.

I agree to carry out all terms of this protocol in accordance with the ICH GCP (Good Clinical Practice) Guidelines, the Declaration of Helsinki and local regulations. I will ensure that the Investigational Medicinal Product is used only as described in the protocol or any subsequent amendment.

I understand that the information/technology contained in this protocol is proprietary and may not be disclosed to any other party, in any form, without prior authorisation from the trial sponsor except to the extent necessary to obtain informed consent from potential trial participants.

[redacted]

[redacted]

PROTOCOL SYNOPSIS

Title:	A multicentre randomised, Double-Blind, Placebo-controlled, Study to evaluate the efficAcy and safety of oral IVErmectin tablets in the prevention of COVID-19 (the SAIVE Trial)
Protocol Number:	mdc-TTG-CT-002
Study Phase:	II
Sponsor:	MedinCell SA
Coordinating Investigator:	Dr. Anna Kostova
Study Objectives:	Primary objective: • To assess the efficacy of ivermectin compared to placebo in the prevention of laboratory-confirmed COVID-19 infection. Secondary objectives: • To assess the efficacy of ivermectin on Time to RT-PCR positive testing. • To assess the efficacy of ivermectin on the occurence of severe COVID-19 symptoms. • To assess the efficacy of ivermectin on Time to first COVID-19 related clinical events. • To assess the efficacy of ivermectin on the rate of COVID-19 related hospitalisations. • To assess the efficacy of ivermectin on the rate of COVID-19 related mortality. • To assess the safety and tolerability of ivermectin given for a period of 28 days.
Study Design:	This is a randomised, double blind, placebo-controlled, multicentric Phase II clinical trial evaluating the efficacy and safety of ivermectin tablets in the prevention of COVID-19 infection. If a person tests positive for SARS-CoV-2 (index case), they can obtain details of this study, in leaflet form, at the clinic or laboratory where they received their positive result. The index case can then provide details of this study to their close contacts. A close contact is defined as: • Anyone who lives in the same household as another person who has tested positive for COVID-19. • Anyone who has had any of the following types of contact with someone who has tested positive for COVID-19: o Face-to-face contact including being coughed on or having a face-to-face conversation within one metre o Been within one metre for one minute or longer without face-to-face contact o Been within 2 metres for more than 15 minutes either as a one-off contact, or cumulatively over a 24-hour period o A person may also be considered a close contact if they have travelled in the same vehicle or plane as a person who has tested positive for COVID-19.

	If the close contact wishes to participate in the study, they should ask the primary contact if they agree to give their informed consent by signing the form attached to the leaflet, through which primary cases agree that information related to their positive testing will be collected as evidence. Then, the contact case should get in touch with the study site and arrange for an appointment for the screening visit (within 5 days after the contact with the index case). At that appointment the contact will be screened, and they will provide the study staff with the index case's signed consent form and positive PCR test result. In addition, informed consent from the close contact must be obtained. If all eligibility criteria are met, the participant (close contact) will be randomised and a loading treatment dose will be administered. Participants will be assigned in a 1:1 ratio to receive oral daily treatment with either ivermectin or placebo. The study requires two visits to the study centre, on Day 1 and Day 28, the first and last days of treatment. In addition, there will be at least 3 remote visits that can be conducted by telephone. The treatment period lasts for 28 days in total, followed by a 28-day follow-up period, and there is a 2-day window period for visits. Therefore, total study duration for each participant is up to 58 days.[redacted]
Study Population:	Healthy volunteers between 18 and 65 years old, self-isolating after being in close contact with an individual who has had a documented exposure to COVID-19 within a maximum of 5 days prior to Screening.
Inclusion Criteria:	Individuals who meet all of the following criteria are eligible to participate in the study: 1. Age between 18 and 65 years, inclusive. 2. Body weight >45 kg. 3. Body Mass Index >18.5. 4. Close contact with a person who has a PCR-confirmed SARS-CoV-2 infection within 5 days before screening. 5. Only one member in the same household will be enrolled. 6. Participants must be able to give informed consent and comply with the study's scheduled events/visits and study assessments. 7. SARS-CoV-2 positive index case must be able to give consent to enable collection of the documented positive PCR test. 8. Female participants of childbearing potential must use a highly effective method of contraception for the duration of the trial. Their male partners should also use a contraception method (i.e condom) unless vasectomized. (Refer to section 4.5 Contraception Requirements). 9. Male participants must use a contraception method (i.e condom) for the duration of the trial, unless vasectomized. Their female partners, if they are of childbearing potential, must use a highly effective method of contraception. (Refer to section 4.5 Contraception Requirements).

Exclusion Criteria:	Individuals who meet any of the following criteria are not eligible to participate in the study: 1. Pregnant or breast-feeding. 2. Participants who have been administered COVID-19 vaccine prior to the inclusion or have a planned vaccination during the duration of the study. 3. A positive COVID-19 result (PCR or antigen test) within 8 days of screening. 4. Presence of typical COVID-19 symptoms (fever >38°C, SpO2 below 93%, dyspnoea, difficulty breathing, chills, repeated shaking with chills, ageusia, anosmia, cough, myalgia, headache) in the past 48 hours prior to screening. 5. Presence of a known uncontrolled/unstable clinically significant medical condition, considered by the investigator as incompatible with study participation. 6. Known history of HIV, HBV and/or HCV. 7. Hypersensitivity to any component of ivermectin. 8. Participants who have been administered ivermectin within 30 days prior to screening. 9. Participation in another interventional trial within the last 30 days or 5 half-lives of the IMP of the other trial, whichever comes first. 10. Having undergone extensive bowel resection which may alter ivermectin absorption. 11. Participants with gastrointestinal erosions and ulcers (e.g. erosive esophagitis, stomach ulcers, ulcerative colitis etc.). 12. Known or clinically suspected disturbance of the blood-brain-barrier (e.g., ABCB-1 [=MDR1] mutation). 13. History of neurotoxicity with ivermectin or other para-glycoprotein (p-gp) substrates or inhibitors. 14. Current use of P-gp inhibitor drugs such as amiodarone, azithromycin, ketoconazole, cyclosporine [redacted] 15. Current use of monoclonal antibodies for the treatment of COVID-19. 16. Known drug or alcohol abuse. 17. Travel to endemic Loa loa regions within the past 3 months prior to screening (central and western Africa). 18. Participants under legal guardianship or trusteeship.
Number of Participants:	400 participants.
[redacted]	
Investigational Medicinal Product:	Ivermectine Substipharm and a matched placebo.
Duration of Participation:	Up to 58 days (28 days of treatment and 28 days of follow-up, with a 2-day window period for visits).
Criteria for Evaluation:	<u>Primary endpoint analysis:</u>

	• RT-PCR tests on D4, D7, D10, and D28, and at any unscheduled visits. Secondary endpoints analyses: • RT-PCR tests on D4, D7, D10, and D28, and at any unscheduled visits. • WHO COVID-19 and News 2 scales scoring on D1, D10, and D28, and at any unscheduled visits. • COVID-19 related AE notification by participants and/or investigators throughout the study. • COVID-19 related hospitalisations notified by the investigators. • Duration of hospitalisation as calculated from the associated SAE notification form (date of hospital admission through to date of hospital release). • COVID-19 related deaths notified by the investigators. • AE notification by participants or detection by investigators.
Concomitant Medication:	Prohibited medications: The following medications are prohibited: • Inhibitors of p-glycoprotien, e.g. amiodarone, azithromycin, ketoconazole, cyclosporine [redacted] up to 28 days prior to randomization and throughout the study. • Current pain medications such as acetylsalicylic acid or metamizol. Precautions: Some medications [redacted] may have moderate or minor interactions with ivermectin.
Endpoints:	Primary endpoint: • Proportion of laboratory-confirmed COVID-19 infections between baseline and Day 28. Secondary endpoints: • Time to change from baseline in negative RT-PCR to positive RT-PCR. • Change from baseline in the WHO-COVID 19 and NEWS-2 scores. • Time to change from baseline to first COVID-19 related clinical events. • Proportion of COVID-19 related hospitalisations. • Proportion of COVID-19 related mortality. • Safety and Tolerability of ivermectin based on treatment emergent adverse events (TEAE) and serious adverse events (SAE) according to Common

	Terminology Criteria for Adverse Events (CTCAE version 5.0).
Statistical Methods:	<u>Sample size:</u> Sample size was calculated to compare the proportion of participants who become positive to SARS-CoV-2 RT-PCR within 1 month after randomisation between the two groups: Placebo group and experimental group receiving ivermectin up to D28. Based on a study assessing the transmission of SARS-CoV-2 infections in households carried out in the US between April and September 2020, the proportion of randomised participants becoming infected in the placebo group is estimated to be 54% (Grijalva et al, 2020).. A difference of 20% is expected between the two groups (OR=2.28). With a power of 90% (1-β) and a significance level of 5% (α), according to the Casagrande & Pike formula the required sample size to detect such difference with a test of comparison of two proportions is equal to 138 participants per arm (Casagrande et al, 1978). A total of 396 participants (198 per arm), rounded up to 400 participants (200 per arm) is required to account for the primary analysis. This sample size also accounts for an estimated dropout rate of 30%. [redacted] <u>Primary endpoint analysis:</u> The comparison of proportion of participants who were tested positive for SARS-CoV-2 up to D28: placebo group versus ivermectin group, will be performed using the Cochran-Mantel Haenszel (CMH) chi-squared test at the two-sided 0.05 level. Two-sided 95% confidence intervals (95% CI) for the proportion differences between groups will be provided. Odds-ratio and corresponding 95% CI will also be reported. The primary endpoint will also be analysed using a logistic regression with treatment group and country as a covariate. Moreover, the analysis of the primary endpoint will be performed for the PP population. [redacted]

	Safety analysis: Safety will be pooled analyses for the Safety set from all centres and countries. Placebo and ivermectin groups will be compared. All adverse events (AEs) will be coded according to coding dictionaries (MedDRA, applicable version) and summarised at System Organ Class (SOC) and Preferred Term (PT) levels. AEs will be classified according to period of occurrence: pre-treatment AEs, treatment-emergent AEs (TEAEs) and post-treatment AEs (PTAEs). AE reporting will focus on TEAEs and PTAEs. Incidence of TEAEs and PTEAEs will be summarised and detailed by seriousness, intensity, action taken with the study medication, other action taken and relationship to study treatment. The number/frequency of participants with TEAEs, related TEAEs, PTAE, the number/frequency of participants with related PTAEs, SAEs and CTCAE grade 3 or more will be displayed by system organ class and preferred term according to MedDRA classification. The frequency of participants with at least one TEAE, PTAE, related PTAE, SAE and/or AE of CTAE grade 3 or more will be compared between treatment groups using a chi-squared test or a Fisher exact test. [redacted]

Table 1: Schedule of Assessments

	Pre Screening	Screening & Randomisation	On-treatment period [(i)]				EOS [(J)]
	D-1 or D1*	**D1**	**D4 (±1 day)**	**D7 (±1 day)**	**D10 (±1 day)**	**EOT-D28** (+2 days)**	**D56 (±2 days)**
	Remote	On-site Visit***	Remote	Remote	Remote	On-site Visit***	Remote
Study participation suitability questionnaire [(a)]	X						
ICF signature [(b)]		X					
Demographics		X					
Medical history		X					
I/C criteria		X					
Treatment dispensation		X					
Treatment administration [(c)]		→	→	→	→	→	
RT-PCR test [(d)]		X	X	X	X	X	
Antigen test [(e)]		X					
Serology [(f)]		X				X	X
NEWS-2 scale		X				X	X	
COVID-19 WHO scale		X				X	X	
Laboratory tests [(g)]		X				X	X
Urine pregnancy test [(g)]		X				X	X
Randomisation [redacted]		X					
Participant diary [(i)]		→	→	→	→	→	
ECG		X				X	
Vital signs		X			X	X	
Adverse Events		⇢	⇢	⇢	⇢	⇢	⇢
Concomitant medication		⇢	⇢	⇢	⇢	⇢	⇢

[redacted]

* Pre-Screening corresponds to the time frame when the first positive case is detected in the cluster within 5 days prior to screening. The study is immediately proposed to the exposed cluster members who might potentially meet the eligibility criteria (Note: only one member in the same household will be enrolled).
** Preferred on-site visit but can be performed remotely according to the investigator's opinion.
*** In case of on-site visit, participants should only use private transport. Moreover, a specific room for participants has to be available and restricted to participants in order to limit their contact with patients.

a) Participants will be questioned about their close contact to the COVID-19 index case, their interest in participating in the study, and will be given information about the study (note that full eligibility inclusion/exclusion criteria will be confirmed once the participant has signed an ICF),

(b) ICF signature for the participant and the index case to collect information regarding his/her SARS-CoV-2 RT-PCR test results,

(c) IMP will be administered as follows: 200 µg/kg as the loading dose admisnistered on D1at the study site, and then 100 µg/kg/day for 27 days taken by the participant at home.

(d) PCR test to be performed on D1, D4, D7, D10 and D28: sequencing and viral load. In addition, any unscheduled test performed by the participant during the study will also be collected. Confirmed negative participants at baseline will continue RT-PCR testing, as per schedule of assessments, until they become positive or reach the planned end of study. When RT-PCR positivity is confirmed, participant will self-isolate according to local requirements.

(e) Participants who have been tested positive at the screening with a quick antigen test will be screen failed. In addition, any unscheduled test performed by the participant during the study will also be collected,

(f) Serology COVID-19 (antibodies levels). In addition, any unscheduled test performed by the participant during the study will also be collected).

(g) Haematology, Biochemistry, Urine pregnancy test [redacted] for details on the parameters evaluated. Pregnancy testing must be highly sensitive, at least before first administration.
[redacted]

(i) Participants will receive their diary on D1 and keep it for the duration of the treatment to record data collected between D1 and D28. They will bring it back to the site on D28.

(J) Additional follow-up remote or on-site unscheduled visits, may be required if deemed necessary by the investigator, notably in case of emerging or prolonged adverse events. During the unscheduled visit, the investigator will evaluate the WHO COVID-19 scale and the NEWS-2 scale, in addition to any assessments deemed necessary.